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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/648,389	08/25/2000	David Pinsky	62683/JPW/JML	5890

7590 07/03/2002

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	19

DATE MAILED: 07/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/648,389	PINSKY ET AL.	
	Examiner	Art Unit	
	Terra Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *2,4 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-7 and 9-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-27 are pending in the instant application.

Nucleotide and/or Amino Acid Sequence Disclosure

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s): The text of the specification discloses nucleotide or amino acid sequences but the application does not contain a copy of the "Sequence Listing" in computer readable form.

Applicant's response to the notice to comply with requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosure in Paper No. 7 filed 2/7/02 is acknowledged. However, although applicant indicated in the response that a disk was submitted, none was entered in the application. Applicant is required to re-submit a CRF of the sequence listing and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

Applicant must fully comply with the sequence rules for any response to this action to be considered fully responsive.

The papers filed on 2/7/02 (certificate of mailing dated 2/7/02) have not been made part of the permanent records of the United States Patent and Trademark Office (Office) for this application (37 CFR 1.52(a)) because of damage from the United States Postal Service irradiation process. The above-identified papers, however, were not so damaged as to preclude

the USPTO from making a legible copy of such papers. Therefore, the Office has made a copy of these papers, substituted them for the originals in the file, and stamped that copy:

COPY OF PAPERS
ORIGINALLY FILED

If applicant wants to review the accuracy of the Office's copy of such papers, applicant may either inspect the application (37 CFR 1.14(d)) or may request a copy of the Office's records of such papers (*i.e.*, a copy of the copy made by the Office) from the Office of Public Records for the fee specified in 37 CFR 1.19(b)(4). Please do **not** call the Technology Center's Customer Service Center to inquiry about the completeness or accuracy of Office's copy of the above-identified papers, as the Technology Center's Customer Service Center will **not** be able to provide this service.

If applicant does not consider the Office's copy of such papers to be accurate, applicant must provide a copy of the above-identified papers (except for any U.S. or foreign patent documents submitted with the above-identified papers) with a statement that such copy is a complete and accurate copy of the originally submitted documents. If applicant provides such a copy of the above-identified papers and statement within **THREE MONTHS** of the mail date of this Office action, the Office will add the original mailroom date and use the copy provided by applicant as the permanent Office record of the above-identified papers in place of the copy made by the Office. Otherwise, the Office's copy will be used as the permanent Office record of the above-identified papers (*i.e.*, the Office will use the copy of the above-identified papers made by the Office for examination and all other purposes). This three-month period is not extendable.

Election/Restrictions

Claims 2, 4 and 8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant's election of Invention II in Paper No. 9 filed 4/29/02 is acknowledged. The traversal is on the grounds that claims of Invention II are not independent of Inventions I and III-

IV and further that the claims of Invention II and Inventions I and III-IV do not define patentably distinct inventions.

Applicant's response/election 09/648,389 (Paper 9, dated 4/29/02) states, "Under M.P.E.P. §802.1, "independent" means "there is no disclosed relationship between the subjects disclosed, that is, they are unconnected in design, operation, and effect".

It is assumed that applicant means M.P.E.P. §802.01. Furthermore, applicant has misquoted M.P.E.P. §802.01. M.P.E.P. §802.01 (August, 2001) properly states: "independent" means that there is no disclosed relationship between the two or more subjects disclosed, that is, they are unconnected in design, operation, or effect."

"The claims of ... Invention II, ... drawn to a method for reducing damage or vascular injury to an ischemic tissue by contacting cells of the tissue with a nucleic acid sequence (antisense sequence) as an inhibitor of Egr-1 protein are related to... Inventions I and III-IV... drawn to a method for reducing damage or vascular injury to an ischemic tissue by contacting cells of the tissue with an organic or inorganic compound, a peptide or an antibody as an inhibitor of Egr-1".

The method for reducing damage or vascular injury to an ischemic tissue by contacting cells of the tissue with a nucleic acid sequence, an organic or inorganic compound, a peptide or an antibody as inhibitors of Egr-1... are methods that are materially different and patentably distinct from each other, as each of these methods requires materials and method steps, technologies and search of a body of prior art, that are distinctly different from those required for each of the others.

Additionally, applicant states: "Under M.P.E.P. §803, the Examiner must examine the application on the merits, even though it includes claims to distinct inventions, if the search and examination of an application can be made without serious burden. There are two criteria for a proper requirement for restriction, namely (1) the invention must be independent and distinct; AND (2) there must be a serious burden on the Examiner if restriction is not required".

Applicant has misquoted M.P.E.P. §803. M.P.E.P. §803 (August, 2001) properly states: "There are two criteria for a proper requirement for restriction, namely (1) the invention must be independent or distinct as claimed; AND (2) there must be a serious burden on the Examiner if restriction is not required".

Distinctness is proven for claims in this relationship if the species are patentably distinct (M.P.E.P. § 806.04(h)).

In the instant case, species are patentably distinct as being methods for reducing damage or vascular injury to an ischemic tissue by contacting cells of the tissue with a nucleic acid sequence, an organic or inorganic compound, a peptide or an antibody as inhibitors of Egr-1 and the inventions are deemed patentably distinct since there is nothing on this record to show them to be obvious variants. Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions anticipated by the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

The method for reducing damage or vascular injury to an ischemic tissue by contacting cells of the tissue with a nucleic acid of Invention II and the methods of Inventions I and III-IV

are related as processes of use. The inventions can be shown to be distinct if: The process for using the product as claimed can be practiced with another materially different product (M.P.E.P. § 806.05(h)). In the instant case, the method for reducing damage or vascular injury to an ischemic tissue by contacting cells of the tissue with a nucleic acid of Invention II can be used as a method for reducing damage or vascular injury to an ischemic tissue by contacting cells of the tissue with an organic compound of Invention I, for example.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art due to their divergent subject matter as shown by their separate classification, their capability of separate use and function, and because the search required for each of the Inventions I-IV is not required for each of the other Inventions, restriction for examination purposes as indicated is proper and final.

Claims 2,4 and 8 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9 filed 4/29/02.

Claims 1, 3, 5-7 and 9-27 are examined as they read on the elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5-7 and 9-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing vascular injury during reperfusion

of an ischemia-induced lung tissue, which comprises contacting the tissue with a nucleic acid of the sequence of SEQ ID NO: 1, which inhibits (antisense) Egr-1 before, during or after reperfusion, does not reasonably provide enablement for a method for reducing vascular injury during reperfusion of an ischemic tissue wherein the tissue is to be transplanted into a subject; wherein the tissue is a lung, a heart, a vein, an artery, a stomach, a colon, a liver, skin, an eye, a pancreas, a brain, a finger, a toe or a limb; wherein the subject has suffered a stroke, or a myocardial infarction; wherein the subject is undergoing angioplasty, cardiac surgery, vascular surgery, or organ transplantation; wherein the vascular surgery is coronary artery surgery.

Claims 1, 3, 5-7 and 9-27 are drawn to or embrace a method for reducing vascular injury during reperfusion of an ischemic tissue, which comprises contacting the tissue with a nucleic acid which inhibits (antisense) Egr-1, before, during or after reperfusion.

The instant invention specification provides general methodologies for determining whether tissue injury in Egr-1 null mice would be diminished in response to lung ischemia/reperfusion.

Lee et al. (Science, 1996, 273:1219-21) disclose that Egr-1 null mice display luteinizing hormone deficiency (LDH) and female infertility. Lee et al. further disclose that Egr-1 influences female reproductive capacity through its regulation of LDH-β transcription (see Abstract).

Topilko et al. (Molecular Endocrinology, 1998, 12:107-22) disclose multiple pituitary and ovarian defects in Egr-1 null mice. Topilko et al. assert, "Egr-1 may have two distinct molecular functions in the anterior pituitary: Transcriptional activation of the LDH-β gene in gonadotropes and control of cell proliferation and/or survival in somatotropes" (see Abstract)

Topilko et al. further disclose that mice homozygous for an Egr-1 mutation have a reduced body size, and both males and females are sterile.

Murphy et al. (Circulation Research, 1999, 84:1469-1470) disclose that accumulation of Na^+ during ischemia and early reperfusion leads, via Na^+/Ca^{2+} exchange, to elevated Ca^{2+}, resulting in myocardial damage (see Abstract).

Medrum (Journal of Surgical Research, 1997, 73:1-13) disclose that as Ca^{2+} increases, the phospholipid hydrolysis required to activated some protein kinase C (PKC) isoforms diminishes (see page 3, first column). Medrum further disclose, ischemia and reperfusion induce myocardial damage, which is likely mediated, in part, by destructive inflammation (see page 7, second column).

Yoshidome et al. (Journal of Surgical Research, 1999, 81:33-37) disclose that ischemia/reperfusion injury may lead to local and systemic organ dysfunction/injury (see Abstract). Yoshidome et al. further disclose that macrophage inflammatory protein-2 (MIP-2) and KC, two potent chemokines, which cause neutrophil activation, exhibit increased expression in a lung ischemia/reperfusion model. Yoshidome et al. assert, "It appears that MIP-2 and KC contribute to lung neutrophil accumulation and the associated pulmonary injury following hepatic ischemia/reperfusion".

Santiago et al. (American Journal of Pathobiology, 1999 155:897-905) disclose that Egr-1 plays an important regulatory role in smooth muscle cell regeneration, but suggest future strategies directed at Egr-1 after injury (page 904, last paragraph). This disclosure appears to indicate that much work needs to be done to elucidate the function of Egr-1 in vascular injury

such that one of ordinary skill in the art would know how to target Egr-1 for reducing vascular injury or ischemia.

The specification as filed shows the effect of lung ischemia/reperfusion on survival times (mortality), arterial oxygenation, myeloperoxidase activity and lung edema (wet to dry weight ratio). These examples fail to show, by correlation, the treatment of reducing vascular injury during reperfusion of an ischemic tissue via Egr-1 antisense inhibition. These examples do not demonstrate that the deleterious effects observed in the prior art above were avoided upon Egr-1 gene knockout or ischemia/reperfusion. For example, the specification is silent on the effect of Egr-1 antisense on male sterility, or female reproductive capacity. The specification is further silent on the levels of Na^+ and Ca^{2+}, the PKC isoforms expressed, the myocardial condition and the expression of the KC chemokine. The specification as filed does not show any direct link, for example, in vascular injury during reperfusion of an ischemic tissue such that contacting the tissue with a nucleic acid which inhibits (antisense) Egr-1, before, during or after reperfusion will reduce damage to the tissue.

The specification as filed does not provide adequate guidance of examples that would show by correlation the practice of the instant invention without the need for undue trial and error experimentation. The specification does not provide a meaningful nexus between an ischemic tissue and contact with an Egr-1 antisense such that interaction will reduce damage to the tissue. It is unpredictable as to whether contact of an ischemic tissue of different lineages (e.g. brain or skin) with an Egr-1 antisense will reduce damage to the tissue. Antisense oligonucleotides are greatly desirable biological agents for reasons well known in the art. However, it is also well-known in the art that the design of antisense oligonucleotides as

therapeutic agents is unpredictable because the biological effects could be non-specific in nature, for example. Furthermore, it is unpredictable that contact of ischemic tissues of different compositions (e.g. epithelial vs. keratinocyte) with an Egr-1 antisense will reduce damage to the tissue.

The unpredictability of the art of antisense therapy in general further adds to the lack of enablement for the current invention. For example, Branch (TIBS Vol 23, February 1998) addresses the unpredictability and the problems faced in the antisense art with the following statements: "Antisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. This is a challenging quest."; "However, their unpredictability confounds research application of nucleic acid reagents."; "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended

clinical use is known, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*."

Jen et al. (Stem Cells, 2000, Vol. 18:307-319) discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al. discuss the advances made in the art but also indicate that more progress needs to be made in the art. In the conclusion of their review, Jen et al. assert, "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "The key challenges to this field have been outlined above. It is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. A large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al. that the state of the art of antisense is

unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

One of ordinary skill in the art would have to engage in undue trial and error experimentation to develop a method for reducing damage to an ischemic tissue, which comprises contacting cells of the tissue with an Egr-1 antisense. In view of the unpredictability of the art, the quantity of experimentation required would include the testing of ischemic tissues from different lineages (e.g. stomach, or eye, or brain), the degree of ischemia (e.g. moderate or extreme) and the variability in contact time that would result in the reduced damage to the ischemic tissue... also to overcome the obstacles to antisense based therapy exemplified in the references cited above. Therefore, undue experimentation would be required of one of ordinary skill in the art to make and use the claimed invention.

It would appear that in view of the above, one of ordinary skill in the art would require specific guidance on how to practice the current invention. The current specification does not provide such guidance and one of ordinary skill in the art would be required to perform undue trail and error experimentation to practice the current invention. The amount of experimentation would include overcoming the obstacle to routine antisense therapies as exemplified in the references discussed above.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9, 11, 15 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated and Santiago et al. (American Journal of Pathobiology, 1999 155:897-905).

Claims 1-9, 11, 15 and 26 are drawn to a method for reducing damage to an ischemic tissue, which comprises contacting the cells of the tissue with a nucleic acid inhibitor (antisense) of Egr-1.

Santiago et al. disclose rat vascular smooth muscle cell (SMC) regrowth after injury is inhibited by directly targeting Egr-1 via antisense (see page 902, first paragraph). Santiago et al further disclose an antisense oligonucleotide (identical to SEQ ID NO: 1) that inhibits Egr-1 (See Santiago et al., Table I). This antisense oligonucleotide contains all of the structural limitations of SEQ ID NO: 1 of the instant invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
June 27, 2002

SEAN McGARRY
PRIMARY EXAMINER